IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2005_1392A
Adrian MERLO et al.	:	**Confirmation No. 3706**
Serial No. 10/549,665	:	Group Art Unit 1618
Filed September 19, 2005	:	Examiner Leah H. Schlientz
RADIOPHARMACEUTICALS FOR CANCER DIAGNOSIS AND TREATMENT	:	**Mail Stop: APPEAL BRIEFS-PATENTS**

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following is Appellants' Brief, submitted under the provisions of 37 CFR § 41.37. Pursuant to the provisions of 37 CFR § 41.20, this brief is submitted with the required fee of $540.00.

I. REAL PARTIES IN INTEREST

The real parties in interest are KANTONSSPITAL BASEL and UNIVERSITAT BERN, the assignees of record, as recorded at Reel 017814 and Frame 0603.

II. RELATED APPEALS AND INTERFERENCES

There are no related prior or pending appeals, interferences or judicial proceedings known to Appellants, Appellants' legal representative, or assignees, which may be related to, directly affect or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The status of the claims is as follows.

Pending Claims: 1-13 and 17-30

Rejected Claims: 17-20 and 29-30

Cancelled Claims: 14-16

Appealed Claims: 17-20 and 29-30

A complete copy of all of the pending claims is provided in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

An Amendment after a Non-Rejection was filed on June 22, 2009, amending claims 29 and 30. Thus, the claims are those set forth in the Amendment filed June 22, 2009.

V. SUMMARY OF CLAIMED SUBJECT MATTER

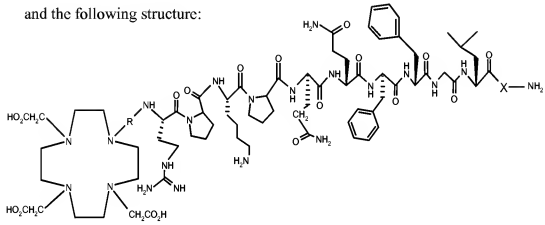
A concise explanation of the subject matter defined in the independent claims involved in the appeal is presented below.

Claim 17 is directed towards a conjugate of

a substance P analogue and a chelator molecule:

(Chelator-R-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-X^{11}-NH_2)

and the following structure:



wherein

R is -CH_2-C(O)-, -$CH(CO_2H)CH_2CH_2$-C(O)- or -$CH(CO_2H)CH_2$-C(O)- and

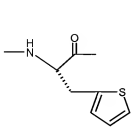
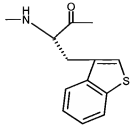
X is -NH-$CH(CH_2CH_2$-SO_2-$CH_3)$-C(O)- (hereinafter abbreviated Met$(O_2)^{11}$), -NH-$CH(CH_2CH_2$-SO-$CH_3)$-C(O)- (hereinafter abbreviated Met$(O)^{11}$), or -NH-$CH[CH(CH_3)CH_2CH_3)$-C(O)- (hereinafter abbreviated Ile^{11}),

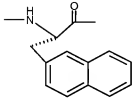
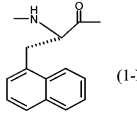
or an analogue of this formula with at least one of the following modifications in the amino acid sequence of substance P analogue:

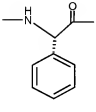
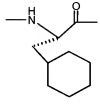
a) replacement of Leu^{10} by -NH-$CH(CH(CH_3)CH_2CH_3)$-C(O)- (hereinafter abbreviated Ile^{10}),

b) replacement of Gly^9 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar^9),

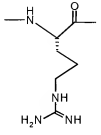
c) replacement of Phe^7 or Phe^8 or both Phe^7 and Phe^8 by a residue of formulae


(2-$Thi^{7,8}$),

(3-Bz$Thi^{7,8}$),

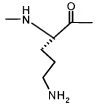

(2-$Nal^{7,8}$),

(1-$Nal^{7,8}$),


(Phegly^{7,8}),

(Cha^{7,8}),

d) replacement of Lys^3 by residue of formulae



(Arg^3), or



(Orn^3),

e) truncation of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5, or

f) replacement of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5 by $-N(CH_3)-CH_2-C(O)-$ (hereinafter abbreviated Sar),

and wherein the conjugate is unlabelled or labeled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dyprosium-162, Dysprosium-165, Dysprosium-167, Holmium-166, Praseodymium-142, Praseodymium-143, Promethium-149, and Terbium-149.

Support can be found on page 3, line 13 to page 5, line 5 of the specification.

Claim 29 is directed towards a method of manufacturing the conjugate of claim 17.

Support can be found on page 16, lines 11-34 as well as in the support given above for claim 17.

Claim 30 is directed towards a method of manufacturing the conjugate of claim 17 wherein X in the formula is $Met(O_2)^{11}$.

Support can be found on page 16, lines 11-34 as well as in the support given above for claim 17.

VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 17-20 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by Visser et al. (WO 92/18536). Also, whether claims 17-20 are unpatentable under 35 U.S.C. § 103(a) as obvious over Visser et al. in view of Coy et al. (US 5,750,646). Finally, whether claims 17-20 and 29-30 are unpatentable under 35 U.S.C. § 103(a) as obvious over Visser et al. in view of Li et al. (Bioconjugate Chem., 2002).

VII. ARGUMENT

The rejection of claims 17-20 under 35 U.S.C. § 102(b) as being anticipated by Visser et al. (WO 92/18536) is respectfully traversed.

The Position of the Examiner

The position of the Examiner, as described in the final Office Action of October 20, 2009, is set forth below.

The Examiner takes the position that a person of skill in the art would immediately envision the claimed compounds from the millions of compounds disclosed in Visser et al. because substance P is known and therefore the only selection would be of $MetO_2$. Further, based on compound 2 disclosed in Visser et al, a skilled artisan would only have to make a selection for A_7.

Appellants' Arguments

Appellants respectfully disagree with the Examiner's position for the following reasons.

The claimed invention relates to a conjugate of a substance P analogue and a chelator molecule. Said conjugate can be used for targeting and treating brain tumors. The conjugate of the claimed invention is labeled or unlabelled and has the structure of formula II (see claim 17) and the abbreviation

Chelator-R-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-X^{11}-NH_2,

wherein

R is -CH_2-C(O)-, -$CH(CO_2H)CH_2CH_2$-C(O)- or -$CH(CO_2H)CH_2$-C(O)- and

X is Met(O_2), Met(O) or Ile;

or has the structure of an analogue of formula II with at least one of the modifications a)-f) in the amino acid sequence.

The conjugates of the claimed invention, which are based on substance P and analogues thereof with chelator DOTAGA, DOTASA or DOTA, are particularly useful for diagnostic investigations, as well as for therapeutic treatment of brain tumors. It was surprisingly found that the claimed radio-labelled conjugates are much more effective than DOTATOC, radio-labelled substance P, substance P analogues, saporin, or other

small radio-labelled peptides with or without chelating agent in targeting and treatment of tumors, especially brain tumors, e,g, gliomas. It was also surprisingly found that metal complex formation was achieved quickly and that the claimed complexes possess a higher chemical stability, thus avoiding contamination of tissue or body fluids with free radio-nuclides. The substance P based radio-labelled conjugates show an unexpectedly high serum half-life time sufficient for application as internal radiodiagnostics and radio-therapeutics. Serum stability of the conjugates with substance P analogues is increased without decreasing the binding affinity to the neurokinine 1 receptor to an undesired extent. In some cases, the binding affinity is even improved when using the substance P analogues. It was also surprisingly found that the claimed substance P based radio-labelled conjugates are capable of diffusing after administration and infiltrating tumor cell nests or satellite lesions, so that they can be detected and treated.

Another aspect of the claimed invention provides a method of targeting brain tumors, localizing or treating brain tumors and satellite lesions thereof in a host, in particular in humans, afflicted with brain tumor, by administrating to the host at least one of the conjugates of the claimed invention.

Visser et al. discloses a method for detecting and localizing tissues having neurokinine 1 receptors by administration of a composition comprising a labelled small peptide having a selective affinity to neurokinine 1 receptors. On page 4 of Visser et al., the general formula (I) for these labelled peptides is indicated, which is:

$$R^1\text{-}A^1{}_m\text{-}A^2{}_n\text{-}A^3{}_o\text{-}Pro_p\text{-}A^4{}_q\text{-}A^5\text{-}\ Phe\text{-}A^6\text{-}A^7\text{-}A^8\text{-}Met(O)_s\text{-}R^2$$

There are:

- nine options for R^1,
-three options for A^1,
- two options for A^2,
- two options for A^3,
- three options for A^4,
- six options for the combinations of m, n, o, p, and q,
- six options for A^5,
- two options for A^6,

- three options for A^7,
- two options for A^8,
- three options for s, and
- at least ten options for R^2,

amounting to several million different combinations. Thus, several million different compounds comprise formula (I).

On the other hand, the claimed invention encompasses only one of these millions of compounds (namely DOTA-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-$Met(O)$-NH_2), which is particularly well suited for the application at issue. In fact, as noted above, the claimed compound has surprising and unexpected properties not taught by the references.

A person skilled in the art cannot find any hint in Visser et al. that would make him or her select the claimed compound among the millions of others disclosed therein. The examples of Visser et al. only describe conjugates comprising DTPA as the chelator moiety, and there is no disclosure in the description that would lead to the above compound. Thus, even if the generic formula (I) of Visser et al. in theory includes the above compound (together with several million others), it fails to particularly teach the species claimed in the present invention. In other words, the claimed species cannot be at once envisioned from the disclosure of Visser et al. as required for a finding of obviousness.

Therefore, the subject-matter of the claimed invention is clearly novel in light of Visser et al and this rejection should be withdrawn.

The rejection of claims 17-20 as unpatentable under 35 U.S.C. § 103(a) as obvious over Visser et al. in view of Coy et al. (US 5,750,646) is respectfully traversed.

The Position of the Examiner

The position of the Examiner, as described in the final Office Action of October 20, 2009, is set forth below.

The Examiner takes the position that a person of skill in the art would immediately envision the claimed compounds from the millions of compounds disclosed in Visser et al. because substance P is known and therefore the only selection would be of $MetO_2$. Further, based on compound 2 disclosed in Visser et al, a skilled artisan would only have to make a selection for A_7. The Examiner further indicates that Coy teaches that Phe and Thi can be interchangeable and therefore it would have been obvious to substitute Thi for Phe at position 7 and/or 8 of the substance P analog of Visser et al. to arrive at the claimed invention.

Appellants' Arguments

Appellants respectfully disagree with the Examiner's position for the following reasons.

It is noted that Coy fails to remedy the deficiencies of Visser set forth above. Namely, Visser is directed towards millions of compounds and fails to specifically teach or suggest the claimed compounds. Further, Coy et al. relates to linear peptide analogues. This reference mentions that non-natural amino acids, such as Thienylalanine (Thi), are interchangeable with Phe. However, since Visser et al. fails to teach all the other limitations of the present invention, combining the teachings of these references do not lead a person skilled in the art to the subject matter of claimed invention.

Thus, withdrawal of this rejection is solicited.

The rejection of claims 17-20 and 29-30 as unpatentable under 35 U.S.C. § 103(a) as obvious over Visser et al. in view of Li et al. (Bioconjugate Chem., 2002) is respectfully traversed.

The Position of the Examiner

The position of the Examiner, as described in the final Office Action of October 20, 2009, is set forth below.

The Examiner takes the position that a person of skill in the art would immediately envision the claimed compounds from the millions of compounds disclosed in Visser et al. because substance P is known and therefore the only selection would be of

$MetO_2$. Further, based on compound 2 disclosed in Visser et al, a skilled artisan would only have to make a selection for A_7. The Examiner further indicates that Visser et al. does not teach reaction of protected substance P analog with DOTA(^{t}Bu)$_3$ as claimed. However, the Examiner contends that Li discloses attachment of DOTA to the D-Tyr^1 residue of somatostatin receptor D-TYr-^{1}-octreotate, allowing radiolabeling with radiohalogens and radiometals. Li further discloses solid phase peptide synthesis using Fmoc methodology. DOTA-tris-(tert-butyl ester) was activated and coupled to Fmoc-protected amino acids. Thus, the Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute DOTA(^{t}Bu)$_3$ as a functional equivalent reactant disclosed in the reaction coupling a chelator to a peptide in Visser.

Appellants' Arguments

Appellants respectfully disagree with the Examiner's position for the following reasons.

It is noted that Li fails to remedy the deficiencies of Visser set forth above. Namely, Visser is directed towards millions of compounds and fails to specifically teach or suggest the claimed compounds. Thus, withdrawal of this rejection is solicited.

For the reasons discussed above, one of ordinary skill in the art would not have arrived at the claimed invention. Thus, the subject matter of Appellants' claims is patentable and the above-rejection should be withdrawn.

Conclusion

For the reasons discussed above, one of ordinary skill in the art would not have arrived at the claimed invention. Thus, the subject matter of Appellants' claims 17-20 and 29-30 is patentable and the above-rejections should be withdrawn. Attached hereto are a Claims Appendix, an Evidence Appendix and a Related Proceedings Appendix.

The brief is submitted with the required fee.

Respectfully submitted,

Adrian MERLO et al.

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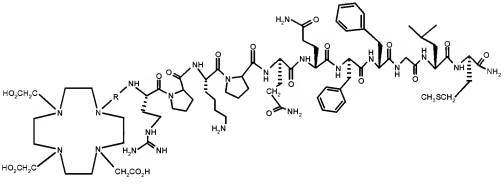
VIII. CLAIMS APPENDIX

Claim 1. (Withdrawn) A method of targeting a brain tumor, localizing or treating a brain tumor or a satellite lesion thereof in a host afflicted with brain tumor, comprising administering to the host a radio-nuclide labelled conjugate of substance P and a chelator molecule, having the abbreviation

Chelator-R-Arg^{1}- Pro^{2}-Lys^{3}-Pro^{4}-Gln^{5}-Gln^{6}-Phe^{7}-Phe^{8}-Gly^{9}-Leu^{10}-Met^{11}-NH_2 and the structure of formula I



(I),

wherein

R is -CH_2-C(O)-, -CH(CO_2H)CH_2CH_2-C(O)- or -CH(CO_2H)CH_2-C(O)-,

or an analogue of formula I with at least one of the following modifications in the amino acid sequence of substance P:

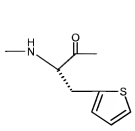
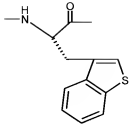
a) replacement of Met^{11} by -NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)- (hereinafter abbreviated Met(O_2)^{11}),

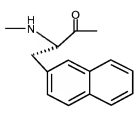
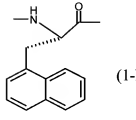
-NH-CH(CH_2CH_2-SO-CH_3)-C(O)- (hereinafter abbreviated Met(O)^{11}), or -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{11}),

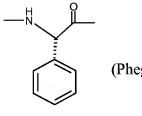
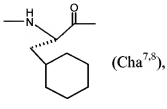
b) replacement of Leu^{10} by -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{10}),

c) replacement of Gly^{9} by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar^{9}),

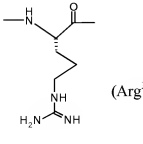
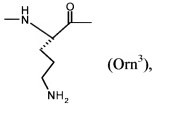
d) replacement of Phe^{7} or Phe^{8} or both Phe^{7} and Phe^{8} by a residue of formulae


(2-Thi^{7,8}),

(3-BzThi^{7,8}),


(2-Nal^{7,8}),

(1-Nal^{7,8}),


(Phegly^{7,8}),

(Cha^{7,8}),

e) replacement of Lys^{3} by residue of formulae


(Arg^{3}), or

(Orn^{3}),

f) truncation of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5, or

g) replacement of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar),

and wherein the conjugate is labelled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dyprosium-162, Dysprosium-165, Dysprosium-167, Holmium-166, Prasedymium-142, Prasedymium-143, Promethium-149, and Terbium-149.

Claim 2. (Withdrawn) The method according to claim 1, wherein the amino acid sequence of substance P is:

a) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2,

b) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met(O_2)-NH_2,

c) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met-NH_2,

d) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met-NH_2,

e) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Gly-Leu-Met-NH_2,

f) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met(O_2)-NH_2,

g) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met(O_2)-NH_2,

h) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Gly-Leu-Met(O_2)-NH_2,

i) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Sar-Leu-Met(O_2)-NH_2,

j) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Sar-Leu-Met-NH_2,

k) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Sar-Leu-Met(O_2)-NH_2

l) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Sar-Leu-Met-NH_2,

m) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Sar-Leu-Met(O_2)-NH_2,

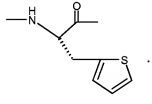
n) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Gly-Leu-Met-NH_2, or

o) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Gly-Leu-Met(O_2)-NH_2.

Claim 3. (Withdrawn) The method according to claim 1, wherein the compound of formula I comprises in the 11-position of the amino acid sequence of the substance P a methionine sulfone residue of formula -NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)- instead of a methionine residue.

Claim 4. (Withdrawn) The method according to claim 1, wherein the glycine residue in position 9 of the amino acid sequence of the substance P is replaced by a sarcosine residue of formula -N(CH_3)-CH_2-C(O)-.

Claim 5. (Withdrawn) The method according to claim 1, wherein the phenylalanine residue in the 7- or 8-position or in both said positions of the amino acid sequence of substance P is replaced by a 3-(2-thienyl)-alanine residue of formula



.

Claim 6. (Withdrawn) The method according to claim 1, wherein the phenylalanine residue in the 8-position of the amino acid sequence of substance P is replaced by a 3-(2-thienyl)-alanine and the glycine residue in position 9 is replaced by a sarcosine residue.

Claim 7. (Withdrawn) The method according to claim 1, wherein the methionine residue in the 11-position of the amino acid sequence of substance P is replaced by a methionine sulfone residue, and the phenylalanine residue in the 8-position is replaced by a 3-(2-thienyl)-alanine residue, or the glycine residue in position 9 is replaced by a sarcosine residue.

Claim 8. (Withdrawn) The method according to claim 1, wherein the amino acid sequence in formula I is:

a) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met(O_2)-NH_2,

b) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met-NH_2,

c) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met-NH_2,

d) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Gly-Leu-Met-NH_2,

e) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met(O_2)-NH_2,

f) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met(O_2)-NH_2,

g) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Gly-Leu-Met-NH_2, or

h) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Sar-Leu-Met(O_2)-NH_2.

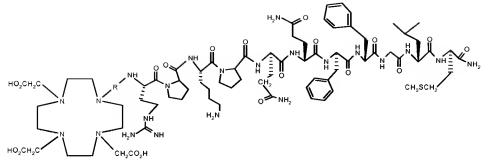
Claim 9. (Withdrawn) The method according to claim 1, wherein the amino acid sequence in formula I is:

a) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met(O_2)-NH_2, or

b) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met(O_2)-NH_2.

Claim 10. (Withdrawn) A method of targeting a brain tumor, localizing or treating a brain tumor or a satellite lesion thereof in a host afflicted with brain tumor, which comprises administering to the host at least one conjugate of substance P and a chelator molecule, having the abbreviation

Chelator-R-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-Met^{11}-NH_2 and the structure of formula I



(I),

wherein

R is $-CH_2-C(O)-$, $-CH(CO_2H)CH_2CH_2-C(O)-$ or $-CH(CO_2H)CH_2-C(O)-$,

or an analogue of formula I with at least one of the following modifications in the amino acid sequence of substance P:

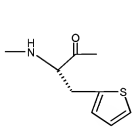
a) replacement of Met^{11} by $-NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)-$ (hereinafter abbreviated $Met(O_2)^{11}$),

$-NH-CH(CH_2CH_2-SO-CH_3)-C(O)-$ (hereinafter abbreviated $Met(O)^{11}$), or $-NH-CH[CH(CH_3)CH_2CH_3)-C(O)-$ (hereinafter abbreviated Ile^{11}),

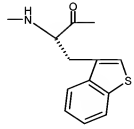
b) replacement of Leu^{10} by $-NH-CH[CH(CH_3)CH_2CH_3)-C(O)-$ (hereinafter abbreviated Ile^{10}),

c) replacement of Gly^9 by $-N(CH_3)-CH_2-C(O)-$ (hereinafter abbreviated Sar^9),

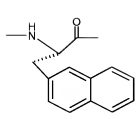
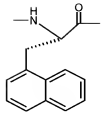
d) replacement of Phe^7 or Phe^8 or both Phe^7 and Phe^8 by a residue of formulae

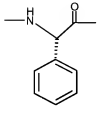
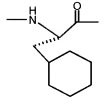


(2-$Thi^{7,8}$),

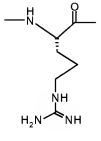
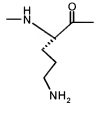


(3-$BzThi^{7,8}$),


(2-Nal^{7,8}),

(1-Nal^{7,8}),


(Phegly^{7,8}),

(Cha^{7,8}),

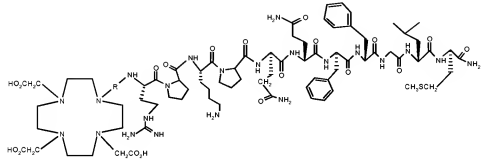
e) replacement of Lys^3 by residue of formulae


(Arg^3), or

(Orn^3),

f) truncation of 1 to 5 amino acids of the sequence Arg^1-Pro^2-Lys^3-Pro^4-Gln^5, or
g) replacement of 1 to 5 amino acids of the sequence Arg^1-Pro^2-Lys^3-Pro^4-Gln^5 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar).

Claim 11. (Withdrawn) A therapeutic or diagnostic method for targeting a brain tumor, localizing or treating a brain tumor or a satellite lesion thereof in a mammal, comprising administering to a mammal in need of such therapy, an effective amount of a radio-nuclide labelled conjugate of substance P and a chelator molecule, having the abbreviation

Chelator-R-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-Met^{11}-NH_2 and the structure of formula I



(I),

wherein

R is -CH_2-C(O)-, -CH(CO_2H)CH_2CH_2-C(O)- or -CH(CO_2H)CH_2-C(O)-,

or an analogue of formula I with at least one of the following modifications in the amino acid sequence of substance P:

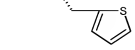
a) replacement of Met^{11} by -NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)- (hereinafter abbreviated Met(O_2)^{11}),

-NH-CH(CH_2CH_2-SO-CH_3)-C(O)- (hereinafter abbreviated Met(O)^{11}), or -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{11}),

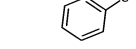
b) replacement of Leu^{10} by -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{10}),

c) replacement of Gly^9 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar^9),

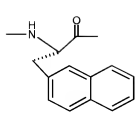
d) replacement of Phe^7 or Phe^8 or both Phe^7 and Phe^8 by a residue of formulae



(2-Thi^{7,8}),



(3-BzThi^{7,8}),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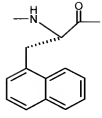
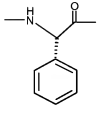
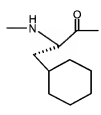
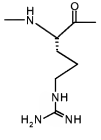
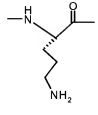

(1-Nal^{7,8}),


(Phegly^{7,8}),

(Cha^{7,8}),

e) replacement of Lys^3 by residue of formulae


(Arg^3), or

(Orn^3),

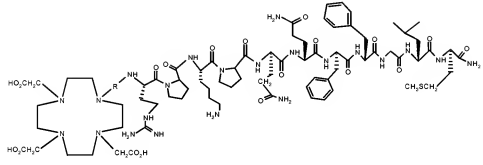
f) truncation of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5, or

g) replacement of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar),

and wherein the conjugate is labelled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90,

Dyprosium-162, Dysprosium-165, Dysprosium-167, Holmium-166, Praseodymium-142, Praseodymium-143, Promethium-149, and Terbium-149.

Claim 12. (Withdrawn) A method of delivering a radio-nuclide labelled substance P conjugate of formula I or an analogue thereof to a host, comprising administering to a host a radio-nuclide labelled conjugate of substance P and a chelator molecule, having the abbreviation Chelator-R-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-Met^{11}-NH_2 and the structure of formula I



(I),

wherein

R is -CH_2-C(O)-, -CH(CO_2H)CH_2CH_2-C(O)- or -CH(CO_2H)CH_2-C(O)-,

or an analogue of formula I with at least one of the following modifications in the amino acid sequence of substance P:

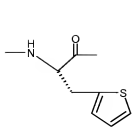
a) replacement of Met^{11} by -NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)- (hereinafter abbreviated Met(O_2)^{11}),

-NH-CH(CH_2CH_2-SO-CH_3)-C(O)- (hereinafter abbreviated Met(O)^{11}), or -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{11}),

b) replacement of Leu^{10} by -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{10}),

c) replacement of Gly^9 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar^9),

d) replacement of Phe^7 or Phe^8 or both Phe^7 and Phe^8 by a residue of formulae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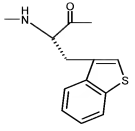
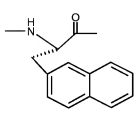

(3-BzThi[7,8]),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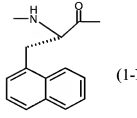
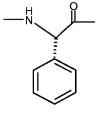
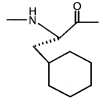
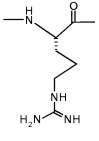
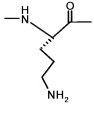

(1-Nal[7,8]),


(Phegly[7,8]),

(Cha[7,8]),

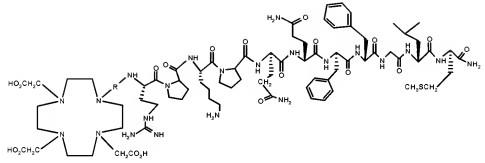
e) replacement of Lys^3 by residue of formulae


(Arg^3), or

(Orn^3),

f) truncation of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5, or

g) replacement of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar),
and wherein the conjugate is labeled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dyprosium-162, Dysprosium-165, Dysprosium-167, Holmium-166, Prascodymium-142, Prascodymium-143, Promethium-149, and Terbium-149.

Claim 13. (Withdrawn) A method for the manufacture of a medicament useful for the detection and therapeutic treatment of a brain tumor or satellite lesion thereof in a mammal, which comprises mixing a radio-nuclide labelled conjugate of substance P and a chelator molecule, having the abbreviation
Chelator-R-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-Met^{11}-NH_2 and the structure of formula I



(I),

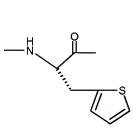
wherein
R is -CH_2-C(O)-, -CH(CO_2H)CH_2CH_2-C(O)- or -CH(CO_2H)CH_2-C(O)-,
or an analogue of formula I with at least one of the following modifications in the amino acid sequence of substance P:
a) replacement of Met^{11} by -NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)- (hereinafter abbreviated $Met(O_2)^{11}$),

-NH-CH(CH_2CH_2-SO-CH_3)-C(O)- (hereinafter abbreviated Met(O)^{11}), or -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{11}),

b) replacement of Leu^{10} by -NH-CH[CH(CH_3)CH_2CH_3)-C(O)- (hereinafter abbreviated Ile^{10}),

c) replacement of Gly^9 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar^9),

d) replacement of Phe^7 or Phe^8 or both Phe^7 and Phe^8 by a residue of formulae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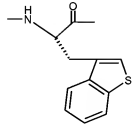
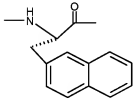
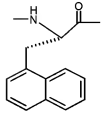
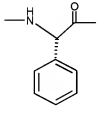
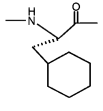

(3-BzThi^{7,8}),

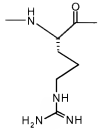
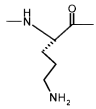

(2-Nal^{7,8}),


(1-Nal^{7,8}),


(Phegly^{7,8}),


(Cha^{7,8}),

e) replacement of Lys^3 by residue of formulae


(Arg^3), or

(Orn^3),

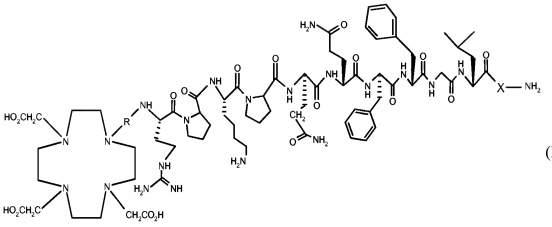
f) truncation of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5, or
g) replacement of 1 to 5 amino acids of the sequence Arg^1- Pro^2-Lys^3-Pro^4-Gln^5 by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar),
and wherein the conjugate is labelled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dyprosium-162, Dysprosium-165, Dysprosium-167, Holmium-166, Praseodymium-142, Praseodymium-143, Promethium-149, and Terbium-149;

with a pharmaceutical carrier.

Claims 14-16. (Cancelled)

Claim 17. (Appealed) A conjugate of a substance P analogue and a chelator molecule, having the abbreviation

Chelator-R-Arg^{1}- Pro^{2}-Lys^{3}-Pro^{4}-Gln^{5}-Gln^{6}-Phe^{7}-Phe^{8}-Gly^{9}-Leu^{10}-X^{11}-NH_2 and the structure of formula II



(II),

wherein

R is -CH_2-C(O)-, -CH(CO_2H)CH_2CH_2-C(O)- or -CH(CO_2H)CH_2-C(O)- and

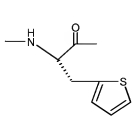
X is -NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)- (hereinafter abbreviated Met(O_2)^{11}), -NH-CH(CH_2CH_2-SO-CH_3)-C(O)- (hereinafter abbreviated Met(O)^{11}), or -NH-CH[$CH(CH_3)CH_2CH_3$)-C(O)- (hereinafter abbreviated Ile^{11}),

or an analogue of formula II with at least one of the following modifications in the amino acid sequence of substance P analogue:

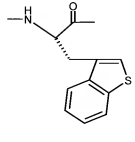
a) replacement of Leu^{10} by -NH-CH($CH(CH_3)CH_2CH_3$)-C(O)- (hereinafter abbreviated Ile^{10}),

b) replacement of Gly^{9} by -N(CH_3)-CH_2-C(O)- (hereinafter abbreviated Sar^{9}),

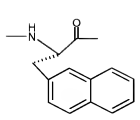
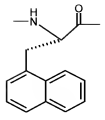
c) replacement of Phe^{7} or Phe^{8} or both Phe^{7} and Phe^{8} by a residue of formulae

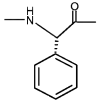
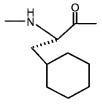


(2-Thi^{7,8}),

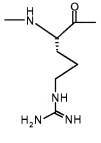
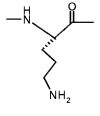


(3-BzThi^{7,8}),


(2-Nal^{7,8}),

(1-Nal^{7,8}),


(Phegly^{7,8}),

(Cha^{7,8}),

d) replacement of Lys^3 by residue of formulae


(Arg^3), or

(Orn^3),

e) truncation of 1 to 5 amino acids of the sequence Arg^1-Pro^2-Lys^3-Pro^4-Gln^5, or

f) replacement of 1 to 5 amino acids of the sequence Arg^1-Pro^2-Lys^3-Pro^4-Gln^5 by -N(CH$_3$)-CH$_2$-C(O)- (hereinafter abbreviated Sar),

and wherein the conjugate is unlabelled or labeled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dyprosium-162, Dysprosium-165, Dysprosium-167, Holmium-166, Praseodymium-142, Praseodymium-143, Promethium-149, and Terbium-149.

Claim 18. (Appealed) The conjugate of claim 17 wherein
X is -NH-CH(CH_2CH_2-SO_2-CH_3)-C(O)- (hereinafter abbreviated $Met(O_2)^{11}$).

Claim 19. (Appealed) A composition comprising at least one pharmaceutical carrier and at least one conjugate according to claim 17.

Claim 20. (Appealed) A composition comprising at least one pharmaceutical carrier and at least one conjugate according to claim 18.

Claim 21. (Withdrawn) A method of targeting a brain tumor or treating a brain tumor in a host afflicted with brain tumor, comprising administering to the host a conjugate of claim 17.

Claim 22. (Withdrawn) A method of targeting a glioma or treating a glioma in a host afflicted with glioma, comprising administering to the host a conjugate of claim 17.

Claim 23. (Withdrawn) A method of targeting a brain tumor or treating a brain tumor in a host afflicted with brain tumor, comprising administering to the host a conjugate of claim 18.

Claim 24. (Withdrawn) A method of targeting a glioma or treating a glioma in a host afflicted with glioma, comprising administering to the host a conjugate of claim 18.

Claim 25. (Withdrawn) The method of claim 21, wherein the conjugate is administered by loco-regional application to a tumor center or into a resection cavity of the host.

Claim 26. (Withdrawn) The method of claim 22, wherein the conjugate is administered by loco-regional application to a tumor center or into a resection cavity of the host.

Claim 27. (Withdrawn) The method of claim 23, wherein the conjugate is administered by loco-regional application to a tumor center or into a resection cavity of the host.

Claim 28. (Withdrawn) The method of claim 24, wherein the conjugate is administered by loco-regional application to a tumor center or into a resection cavity of the host.

Claim 29. (Appealed) A method for the manufacture of a radiopharmaceutical or radiodiagnostic formulation useful for targeting a brain tumor or treating a brain tumor in a host afflicted with brain tumor, which comprises

(a) preparing a suitable substance P analogue in a side chain protected form by solid phase peptide synthesis;

(b) coupling the side chain protected substance P analogue with a prochelator selected from the group consisting of DOTAGA(^{t}Bu)$_4$, DOTASA(^{t}Bu)$_4$, and DOTA(^{t}Bu)$_3$ to obtain a protected conjugate;

(c) cleaving the protected conjugate from resin and removing the protection groups to obtain an unlabelled conjugate of claim 17; and

(d) labeling the unlabelled conjugate with a radionuclide to obtain a labeled conjugate of claim 17.

Claim 30. (Appealed) A method for the manufacture of a radiopharmaceutical or radiodiagnostic formulation useful for targeting a brain tumor or treating a brain tumor in a host afflicted with brain tumor, which comprises

(a) preparing a suitable substance P analogue in a side chain protected form by solid phase peptide synthesis;

(b) coupling the side chain protected substance P analogue with a prochelator selected from the group consisting of DOTAGA(^{t}Bu)$_4$, DOTASA (^{t}Bu)$_4$, and DOTA (^{t}Bu)$_3$ to obtain a protected conjugate;

(c) cleaving the protected conjugate from resin and removing the protection groups to obtain an unlabelled conjugate of claim 18; and

(d) labeling the unlabelled conjugate with a radionuclide to obtain a labeled conjugate of claim 18.

IX. EVIDENCE APPENDIX

None

X. RELATED PROCEEDINGS APPENDIX

None